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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,834	04/15/2004	Fredrik C. Kamme	PRD2047NP	2975

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EXAMINER	
WHISENANT, ETHAN C	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/826,834	KAMME ET AL.	
	Examiner	Art Unit	
	Ethan Whisenant, Ph.D.	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *5-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

NON-FINAL ACTION

1. **CLAIMS 1-19** is/are pending.

SEQUENCE RULES

2. This application complies with the sequence rules and the sequences have been entered by the Scientific and Technical Information Center.

ELECTION/RESTRICTION

3. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. **Claim(s) 1-4** drawn to a method of, classified in Class 435, subclass 6.

II. **Claim(s) 5-19** drawn to a method of, classified in Class 435, subclass 6.

4. The inventions are distinct, each from the other for the following reasons.

Groups I and II are distinct inventions because the two methods comprise different intermediate steps. Note that Group I comprises steps wherein a RNA precipitate is formed and wherein a RNA -preserved biological sample is histochemically stained. These limitations are not found in Group II.

5. Because these inventions are distinct for, at least, the reasons given above and the necessity for a non-coextensive literature search, restriction for examination purposes as indicated is proper.

6. During a telephone conversation with Linda Evans on 23 MAR 05 a provisional election was made with traverse to prosecute the invention of Group I, Claims 1-4. Affirmation of this election must be made by applicant in responding to this Office action. Claims 5-19 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligations under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

CLAIM REJECTIONS UNDER 35 USC § 103

9. **Claim(s) 1-4** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Rimm et al.[US 2002/0177149] in view of Reiter et al. [2002/0102666].

Claim 1 is drawn to a method of analyzing a biological sample which method comprises four steps. To begin, the RNA in the biological sample is preserved by incubating the biological sample with an RNA preservative in an aqueous solution so as to precipitate RNA. Next, the RNA-preserved biological sample is histochemically stained. Then the biological sample is histochemically analyzed to identify specific cell populations, and finally, the mRNA expression pattern of the identified cells is analyzed by a method comprising: in-situ hybridization or isolating identified cells and subjecting the isolated cells to bioarray gene profiling.

Rimm et al. teach a method of analyzing a biological sample comprising all of the limitation(s) recited in Claim 1 except these authors do not explicitly teach histochemically analyzed the biological sample in order to identify specific cell populations. However, these authors do teach detecting nucleic acid (i.e. mRNA) biomarkers of neural tissue and tumors using *in situ* hybridization. In addition,

Reiter et al. teach identifying cancer cells which overexpress PSCA mRNA via via *situ* hybridization, see, at least, for example, paragraphs [240] and [305]. Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method taught by Rimm et al. wherein PSCA mRNA is used to identify prostate cancer cells (e.g. micrometastatic prostate cancer) in biopsy samples as suggested by Reiter et al. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose.

As regards the limitation in Claim 1 which reads "so as to precipitate RNA" the examiner contends that this limitation is inherent to both of Rimm et al. and Reiter et al. Note that in both of these references the mRNA is immobilized (i.e. precipitated) on the slide prior to *in situ* hybridization analysis. Also note, *In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)* wherein it was stated "Something which is old does not become patentable upon the discovery of a new property." The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.

Claim 2 is drawn to an embodiment of Claim 1 wherein the RNA preservative is selected from a defined group which includes: triphenylmethane dyes, cresyl violet, polyamines, and cobalt ions.

Rimm et al. in view of Reiter et al. teach all of the limitations recited in Claim 2 except these authors do not explicitly teach in their examples or preferred embodiments using any of the RNA preservatives recited. However, these authors do teach that conventional methodologies for ISH, hybridization and probe selection were used as described, for example, in Leitch, et al. *In Situ* Hybridization: a practical guide, Oxford BIOS Scientific Publishers, Microscopy Handbooks v. 27 (1994). Furthermore, Rimm et al. teach methyl green - a triphenylmethane dye - as one of a laundry list of suitable dyes for use as a stain or counterstain in *in situ* hybridization, see, at least, for example, paragraph [0106] of Rimm et al. Although these authors are silent as regards the RNA preservation properties of this dye, this characteristic is considered to be inherent to the methyl green of Rimm et al. Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method reasonably suggested by the combination of Rimm et al. in view of Reiter et al. wherein methyl green is used as a stain or counterstain. The motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose.

Claim 3 is drawn to an embodiment of Claim 1 wherein the RNA preservative is a triphenylmethane dye selected from the group consisting of methyl green, crystal violet, and pararosaniline.

Rimm et al. in view of Reiter et al. teach a method of analysis comprising all of the limitations recited in Claim 3 except these authors do not explicitly teach in their examples or preferred embodiments using any of the RNA preservatives recited. These authors teach that conventional methodologies for ISH, hybridization and probe selection were used, as described, for example, in Leitch, et al. *In Situ* Hybridization: a practical guide, Oxford BIOS Scientific Publishers, Microscopy Handbooks v. 27 (1994). However, Rimm et al. do teach methyl green as part of a laundry list of possible stain or counterstain for use in their method, see, at least, for example, paragraph [0106] of Rimm et al. Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method reasonably suggested by the combination of Rimm et al. in view of Reiter et al. wherein methyl green is used as a stain or counterstain. The motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose.

As regards the limitation that the triphenylmethane dyes recited act as "RNA preservatives," the examiner contends that this limitation is inherent to the methyl green of Rimm et al.

Claim 4 is drawn to an embodiment of Claim 1 wherein histochemically analyzing comprises subjecting the biological sample to a histochemical assay selected from a defined group which includes *in situ* hybridization for detecting mRNA

Both of Rimm et al. and Reiter et al. teach this/these limitation(s), see, at least, for example, paragraph [0106] of Rimm et al. and/or paragraphs [240] and [305] of Reiter et al.

10. Claim(s) 2 is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Rimm et al.[US 2002/0177149] in view of Reiter et al. [2002/0102666] as applied against Claim 1 above, and further in view of Lader [US 6, 204,375 (2001)] and/or Willson III et al. [2002/0197637]

Claim 2 is drawn to an embodiment of Claim 1 wherein the RNA preservative is selected from a defined group which includes: triphenylmethane dyes, cresyl violet, polyamines, and cobalt ions.

Rimm et al. in view of Reiter et al. teach all of the limitations recited in Claim 2 except these authors do not explicitly teach in their examples or preferred embodiments using any of the RNA preservatives recited. However, these authors do teach that conventional methodologies for ISH, hybridization and probe selection were used as described, for example, in Leitch, et al. *In Situ* Hybridization: a practical guide, Oxford BIOS Scientific Publishers, Microscopy Handbooks v. 27 (1994).

CONCLUSION

11. **Claim(s) 1-4** is/are rejected and/or objected to for the reason(s) set forth above.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ethan Whisenant, Ph.D. whose telephone number is (571) 272-0754. The examiner can normally be reached Monday-Friday from 8:30AM -5:30PM EST or any time via voice mail. If repeated attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (571) 272-0745.

The fax number for this Examiner is (571) 273-0754. Before faxing any papers please inform the examiner to avoid lost papers. Please note that the faxing of papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

ETHAN WHISENANT
PRIMARY EXAMINER

Art Unit 1634

Furthermore, Rimm et al. teach methyl green - a triphenylmethane dye - as one of a laundry list of suitable dyes for use as a stain or counterstain in *in situ* hybridization, see, at least, for example, paragraph [0106] of Rimm et al. Although these authors are silent as regards the RNA preservation properties of this dye, this characteristic is considered to be inherent to the methyl green of Rimm et al. In addition, Lader teaches utilizing an RNA preservation medium which comprises a salt that precipitates the RNA in a sample along with the cellular proteins. One of the salts taught by Lader as useful in their RNA preservation medium is cobalt sulfate (i.e. cobalt ions). Furthermore, Willson III et al. teach using polyamines, trivalent and tetravalent metal ions [(i.e. cobalt ions) hexammine cobalt, chloropentamine cobalt] to preserve nucleic acids in a biological sample. In view of these findings and absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method reasonably suggested by the combination of Rimm et al. in view of Reiter et al. wherein at least one of the RNA preservation reagents taught by Lader and/or Willson III et al. is utilized. The motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Furthermore, the ordinary artisan would have been motivated to utilize the RNA preservation medium of Lader and/or Willson III et al. in order to prevent RNA degradation prior to *in situ* hybridization.